them emptying into the internal saphenous vein by the time the knee is reached. Frequent enlarged tortuous communicating branches are seen extending from the saphenous apparently fading into the soft tissues. It is in this type of case that the venogram is probably of the greatest value. Clinically one sees dilated superficial veins and clinical tests may be difficult to interpret or actually misleading. A carefully done venogram studied in the light of the clinical findings in the patient may be of the utmost help in properly handling the patient.

The diagnosis of thrombosis by venography can be almost absolute, when the clot is seen in the vein outlined by the opaque material. Occasionally this finding may be critical in proving the site of origin for emboli.

Venography has a place of real though limited value among medical procedures. It should be used with a full understanding of its difficulties, its use should be limited to cases where the indications are clear, and the results should be critically analyzed in view of clinical condition of the patient.

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HYPOPARATHYROIDISM*

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IMPAIRED parathyroid function may become a major consideration following thyroidectomy. Symptoms of hypoparathyroidism may range from the dramatic acute tetany with epileptiform convulsions, to the more common chronic or latent form often characterized by a variety of psycho-motor and metabolic disturbances. Early recognition and prompt treatment is of the utmost importance, especially in the acute phase of the disease. Fortunately, specific therapy for the disorder has been developed and is available.

INCIDENCE

The incidence of acute hypoparathyroid tetany is low, varying from .2 per cent to 2.0 per cent in the larger thyroid clinics. In our last 1,000 cases, the incidence was .2 per cent. The chronic or latent form occurs more frequently and may be readily overlooked. A survey of 100 of our thyroid cases operated upon ten years ago, revealed an incidence of about 15 per cent of mild hypoparathyroidism. In our more recent 100 cases, the rate had dropped to 9 per cent. The factors that contribute to a low incidence of hypoparathyroidism are chiefly the technical operative procedures designed at preserving the parathyroid bodies and their blood supply. Among these may be listed the maintenance of a posterio-lateral leaf at the time of the thyroidectomy, and minimal suturing of the residual remnant of the gland. Routine ligation of the inferior thyroid artery, which is the main source of the blood supply to the parathyroid glands, may also dangerously impair their activity. Undue trauma, such as occurs frequently in operations for recurrent goiters, may easily damage or completely destroy the parathyroids. About 60 per cent of our patients operated upon for recurrent or residual goiter ultimately developed symptoms

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of latent or mild hypoparathyroidism. In one of these cases, recurring attacks of acute tetany with epileptiform convulsions followed the fifth thyroidectomy.

SYMPTOMS

The most striking clinical feature of hypoparathyroidism is the dramatic symptom complex known as tetany. This may manifest itself usually two or three days after thyroidectomy by the sudden appearance of epileptiform convulsions, muscular rigidity, stridor, and dyspnea. Milder premonitory symptoms usually precede the convulsions by six to twenty-four hours, and the close observer, may serve as a warning of the impending attack. The patient will be wakeful, anxious, and appear unusually quiet. The forehead becomes glazed, and flushing of the face with circumoral palor will be noted. Numbness and tingling of the extremities, together with early signs of carpo-pedal spasm gradually appear. A positive Chvostek sign establishes the diagnosis. In most cases the acute attack is transitory, lasting but a few days or weeks, until the remaining parathyroid glands slowly regain their function. Occasionally the parthyroid damage is extensive and the patient passes into a state of permanent chronic hypoparathyroidism in which acute tetany may appear at varying intervals. Rarely, in an untreated case, death will occur in an acute attack.

Chronic, mild, or latent hypoparathyroidism appears weeks or even months after operation. This more common form may even go unrecognized, especially if the patient disappears from the surgeons observation. The slow insidious development of symptoms probably is the result of atrophy from impaired blood supply, or the pressure of scar tissue formation that gradually diminishes the glandular function. A great variety of symptoms may appear incident chiefly to the resultant hypocalcemia. Among the more important symptoms will be weakness, fatigue, and loss of energy. Numbness and tingling of the extremities with muscle cramps and stiffness may predominate. At times, the muscle stiffness becomes severe, causing the tissues to assume a board-like firmness with functional incapacitating impairment. Chvostek's and Trousseaus's signs remain constant. Less commonly, lenticular cataract, trophic changes, and disturbances of calcium metabolism develop, giving rise to an impressive list of variegated symptoms, often erroneously classified as functional nervous disorders.

TREATMENT

In acute post-thyroidectomy tetany, particularly in the event of sudden epileptiform convulsions, prompt action is imperative. There probably will not be time for serum calcium determinations. In this alarming emergency, specific action can be obtained by injections of parathyroid extract together with calcium salts. The initial dosage of the parathyroid extract should be 1 cc. or 100 units, best given intramuscularly, and an intravenous injection of 10 cc. of 10 per cent calcium gluconate. Thereafter, .5 cc. of the extract should be given once or twice daily until the serum calcium and phosphorus levels approach normal. To attain maximum effect, the hormone injections must be supplemented by calcium and at this time oral administration will suffice. Estimations of the serum calcium level will determine the necessary dosage. For some unknown reason parathyroid extract alone will not produce a normal serum calcium-phosphorus balance. The continuous use of the hormone soon causes a state of tolerance or refractivity with gradually diminishing effect until ultimately the favorable action will be completely lost. This state of refractivity may be due to the development of antibodies in the blood stream or to a local fixation tendency at the site of injection thus preventing absorption. For this reason parathyroid extract cannot be used effectively in the treatment of chronic hypoparathyroidism. Difficulty of administration and economic factors also enter into this problem. In the management of chronic hypoparathyroidism the great majority of patients may be controlled adequately by calcium alone, the dosage varying with the severity of symptoms and the degree of hypocalcemia. There will remain a small group of cases in which calcium is only partially effective. Some benefit may be obtained by diet high in calcium but such diets usually also are high in phosphorus which tends to disturb the desired serum calcium-phosphorus ratio.

Homologous parathyroid transplants have been attempted numerous times but rarely if ever has this procedure been of value. One such patient came to our attention recently in whom parathyroid glands had been transplanted into both pectoral muscles. There was no temporary or permanent improvement in the patient's symptoms.

In these difficult cases where the simpler remedies are ineffective, dihydrotachysterol has almost specific action. This substance, developed in Germany by Holtz was formerly called A.T. 10 but now it is manufactured in this country under the name of Hytakerol. Its specific action in chronic hypoparathyroidism is similar to that of parathyroid extract in acute tetany but it differs from the hormone in several ways. Its action is much slower, requiring two to three days to initiate a rise in the serum calcium level and it does not tend to induce in the patient a gradually increasing tolerance. On the contrary, there is some evidence to show that it has cumulative action. Its slow action makes it unsuitable for emergency use in acute hypoparathyroidism but it has been found to be highly effective in preventing recurring attacks of acute tetany. The correct dosage is most important and this must be worked out in each individual. Over dosage can easily cause a hypercalcemia which may induce a variety of distressing symptoms and even death. The chief side effects of over dosage are weakness, nausea,

and vomiting, diarrhea, headache, vertigo, stuper, polyuria, and ataxia.

The usual initial dose of Hytakerol is 1 cc. to 2 cc. daily supplemented by calcium salts. As the serum calcium level rises, the dose is decreased until a maintenance dose is established. This may vary from .5 cc. daily to .5 cc. or less weekly. One patient in our series states that she requires only one drop of Hytakerol twice a week. After the first day or two, serum calcium determinations will not be necessary and the patient can then be instructed to make his own determinations by the simple Sulkowitch test for calicum in the urine. Even this test can be discarded and the patient gradually learns to adjust his Hytakerol and calcium dosage by subjective symptoms alone. Other sterols such as Vitamin D and D_2 tend to raise the serum calcium level but none gives the satisfactory specific action that can be obtained from Hytakerol.

Many patients who develop postoperative hypoparathyroidism also show evidence of hypothyroidism. In these cases, general improvement results from thyroxin or thyroid extract but it is doubtful if these agents directly or indirectly influence the serum calcium concentration.

In conclusion it should be stated that for reasons of simplicity certain phases of the hypoparathyroid problem have been omitted from this discussion. A consideration of the rare idiopathic hypoparathyroidism, alkalosis tetany, and such factors as the relationship of acute infections or pregnancy to calcium and phosphorus metabolism would tend to confuse the picture, and had best be left in the realm of the internist and the endocrinologist.

A few of the more important practical considerations in connection with hypoparathyroidism will bear emphasis.

1. Impending acute convulsive tetany may be averted by the recognition and treatment of certain warning premonitory symptoms.

2. In the acute attack the specific action of parathyroid extract makes it the most effective therapeutic agent. A tendency to induce tolerance precludes its prolonged use.

3. Symptoms of chronic hypoparathyroidism often may be vague and easily can be overlooked by the casual observer.

4. Hytakerol, while too slow in its action for use in acute tetany, is the ideal remedy in the treatment of chronic hypoparathyroidism.

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Use of the Anti-Coagulants, Heparin and Dicumarol*

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IN the young and vigorous person, under normal conditions the blood remains fluid *in vivo*. With advancing age, the tendency for the blood to clot *in vivo* without apparent cause is not an uncommon phenomenon. Under circumstances of trauma, accidental or surgically induced, the tendency for the blood to coagulate is enhanced both *in vivo* and *in vitro*. In the attempt to combat abnormal coagulation of the blood *in vivo*, it is necessary to choose and to employ the proper anticoagulant. The three important questions concerning the problem of thrombosis are:

1. What evidence can be brought to show that an increased tendency to thrombus formation exists?

2. When and under what circumstances will thrombosis occur?

3. Will anti-coagulants prevent the formation of thrombi and will they have any effect on thrombi already formed?

Thrombosis is one manifestation of a diffuse and generalized alteration in the mechanism of the coagulation of the blood. When venous thrombosis occurs, an active program of treatment is necessary in order that further thromboses and possible pulmonary embolism may be prevented. The question naturally arises, will one ligate the affected vessels, keeping in mind that the tendency to thrombus formation is not a localized condition, or will one use the anti-coagulants? We must remember that ligating a thrombosed vessel does not influence the formation of venous thrombi elsewhere, although it does prevent a pulmonary embolus from originating in the distal part of the ligated vein. On the other hand, when anti-coagulants are used, they do tend to interfere with the formation of freely floating and pedunculated thrombi from which emboli may break off, although they do not dissolve thrombi already formed.

In vivo the fluidity of the blood is maintained by an intact, untraumatized vascular endothelium and the presence of fluidifying agents such as anti-thromboplastin, anti-thrombin, and fibrinolysin. On the other hand, the coagulation of the blood *in vivo* is enhanced by damage to the vascular endothelium, excesses of thromboplastin from traumatized tissue, destroyed leukocytes and disintegrated blood platelets, and from increased quantities of prothrombin, and possibly calcium and fibrinogen. A simplified test for the detection of subjects who may have an increased tendency to intravascular coagulation of the blood has been proposed[1]. For this purpose 10 mgm. (1.0 cc.) of heparin are injected intravenously. The coagulation time of the whole blood is determined before injection and at 10, 20, 30 and 40

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